PATENT
Customer Number: 22,852
Attorney Docket No. 3260.0047-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
John Ernest SIMS	)	Group Art Unit: 1646
	)	
Serial No.: 09/612,921	)	Examiner: O. Chernyshev
	)	
Filed: July 10, 2000	)	
	)	

For: IL-1 Delta DNA AND POLYPEPTIDES

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

Sir:

DECLARATION UNDER 37 C.F.R. § 1.132

I, John E. Sims, do hereby declare as follows:

2. I am currently employed as a Distinguished Fellow in the Department of Molecular Immunology of Immunex Corporation, a wholly-owned subsidiary of Amgen Inc. I received a Ph.D. degree from Harvard University in Biochemistry; a copy of my curriculum vitae is attached hereto as Exhibit 1. I am the inventor of the subject matter disclosed and claimed in the above-identified patent application.

3. I have read U.S. Application No. 09/612,921 ("the '921 application"), a copy of which is attached hereto as Exhibit 2.

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4. On page 37, lines 2-9, the application (Exhibit 2) states:

Human IL-1 delta gene maps to chromosome 2q11-12. All or a portion of the nucleic acids of SEQ ID NO:3, including oligonucleotides, can be used by those skilled in the art using well-known techniques to identify human chromosome 2, and the specific locus thereof, that contains the DNA of IL-1 delta family members. Useful techniques include, but are not limited to, using the sequence or portions, including oligonucleotides, as a probe in various well-known techniques such as radiation hybrid mapping (high resolution), in situ hybridization to chromosome spreads (moderate resolution), and Southern blot hybridization to hybrid cell lines containing individual human chromosomes (low resolution).

5. On page 37, lines 24-32, the application (Exhibit 2) states:

As set forth above, SEQ ID NO:3 has been mapped to the 2q11-12 region of chromosome 2. Human chromosome 2 is associated with specific diseases which include but are not limited to glaucoma, ectodermal dysplasia, insulin-dependent diabetes mellitus, wrinkly skin syndrome, T-cell leukemia/lymphoma, and tibial muscular dystrophy. Thus, the nucleic acid of SEQ ID NO:3, or a fragment thereof, can be used by one skilled in the art using well-known techniques to analyze abnormalities associated with gene mapping to chromosome 2. This enables one to distinguish conditions in which this marker is rearranged or deleted. In addition, nucleotides of SEQ ID NO:3 or a fragment thereof can be used as a positional marker to map other genes of unknown location.

6. Based on the above passages from the application, I understand that:

(1) the human IL-1 delta gene maps to the 2q11-12 region of chromosome 2;

(2) abnormalities of human chromosome 2 are associated with specific diseases; and

(3) SEQ ID NO:3 or a fragment thereof can be used with *in situ* hybridization to chromosome spreads to detect rearrangements of the proximal region of chromosome 2 associated with specific diseases and abnormalities.

7. Based on the fact that the human IL-1 delta gene maps to the 2q11-12 region of chromosome 2, I would expect that SEQ ID NO:3 or a fragment thereof can be used with *in situ* hybridization to chromosome spreads to detect rearrangements of the

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proximal region of chromosome 2 associated with specific diseases and/or abnormalities.

8. Based on my experience in molecular biology, it is my opinion that SEQ ID NO:3 and fragments thereof would hybridize to a specific locus in the proximal region of chromosome 2. In this way, SEQ ID NO:3 and fragments thereof provide a marker for a specific region of chromosome 2.

9. Based on my experience in molecular biology, it is my opinion that hybridization to the human IL-1 delta gene on chromosome 2 under conditions of high stringency is a property that is specific to SEQ ID NO:3, fragments thereof and other IL-1 delta nucleic acid molecules. This property is not possessed by every nucleic acid molecule. Rather, it is a specific property possessed by very few nucleic acid molecules (namely, SEQ ID NO:3, fragments thereof, and other IL-1 delta nucleic acid molecules). This is because nucleic acid molecules hybridize to other nucleic acid molecules based on their unique nucleic acid sequence. The unique nature of polynucleotides comprising SEQ ID NO:3 or a fragment thereof allows them to specifically hybridize to their complementary nucleic acid sequence under conditions of high stringency, under which other nucleic acid molecules would not hybridize.

10. Based on the above facts, I conclude that the use of SEQ ID NO:3 or a fragment thereof to detect rearrangements of the human IL-1 delta gene on chromosome 2 is a use that is specific to SEQ ID NO:3 and fragments thereof.

11. Based on the above facts, I also conclude that the use of SEQ ID NO:3 or a fragment thereof to detect rearrangements of the human IL-1 delta gene on chromosome 2 can be practiced without the need for any additional research.

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Accordingly, SEQ ID NO:3 or a fragment thereof can be used with *in situ* hybridization to chromosome spreads to detect cytogenetic rearrangements of the proximal region of chromosome 2 without the need for any additional research.

12. I have read an article by Mu et al., *Journal of Medical Genetics*, 1984, 21:57-71, a copy of which is attached hereto as Exhibit 3. Mu et al. examined a patient with various abnormalities and found an abnormal proximal long arm of chromosome 2. Mu et al. at 57, Summary. The patient in Mu et al. was suffering from numerous physical abnormalities. *Id.* at 57. The authors determined that there was a tandem duplication of 2q11.2-q14.2. *Id.* Based on Mu et al., I understand that the patient had a rearrangement (specifically, a tandem duplication) of the proximal region of chromosome 2, which was associated with numerous physical abnormalities.

13. Because of the specificity with which SEQ ID NO:3 or a fragment thereof hybridizes to the specific locus on chromosome 2, I conclude that SEQ ID NO:3 or a fragment thereof can be used for *in situ* hybridization of chromosome spreads to detect the rearrangement described by Mu et al. That is, SEQ ID NO:3 or a fragment thereof can be used to determine the presence of normal chromosome 2 sequences on one of the chromosomes and for detecting the existence of the duplicated region of the abnormal chromosome in the patient described in Mu et al.

14. Based on Mu et al., on the teachings of the instant application, and on my knowledge of molecular biology, I would expect that SEQ ID NO:3 or a fragment thereof could be successfully used with *in situ* hybridization to chromosome spreads from other patients to detect rearrangements of the proximal region of chromosome 2 similar to that described Mu et al.

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15. I have read an article by Glass et al., *Journal of Medical Genetics*, 1998, 35:319-322, a copy of which is attached hereto as Exhibit 4. Glass et al. examined two patients (mother and child) with various abnormalities, and found an abnormal chromosome 2. Glass et al. at 319. The patients in Glass et al were suffering from numerous physical abnormalities. *Id.* Using fluorescence *in situ* hybridization (FISH), the authors determined that the patients had a proximal 2q trisomy (2q11.2-q21.1). *Id.* FISH showed an insertion of chromosome 2-derived material into the middle of the short arm of chromosome 8. *Id.* at 320, Figure 4.

16. Based on Glass et al. and on the disclosure of the present application, I conclude that SEQ ID NO:3 or a fragment thereof could be used FISH analysis of chromosome spreads from these patients to detect the proximal 2q trisomy described in Glass et al. That is, SEQ ID NO:3 or a fragment thereof could be used to determine the presence of normal chromosome 2 sequences and for detecting the insertion of material derived from chromosome 2 into chromosome 8 as described by Glass et al.

17. Based on Glass et al., on the above passages from the application, and on my knowledge of molecular biology, I would expect that SEQ ID NO:3 or a fragment thereof could be successfully used with FISH analysis of chromosome spreads from other patients to detect rearrangements of the proximal region of chromosome 2 similar to those described in Glass et al.

18. Based on Mu et al., on Glass et al., and on my experience in molecular biology, it is my opinion that the detection of cytogenetic rearrangements associated with chromosome 2, such as those associated with physical abnormalities in Mu et al.

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and Glass et al., is a real world use for IL-1 delta nucleic acids, including SEQ ID NO:3 and fragments thereof.

19. Based on Mu et al., on Glass et al., and on my experience in molecular biology, it is my opinion that the detection of rearrangements associated with chromosome 2 provides a public benefit by facilitating the diagnosis of patients with chromosomal rearrangements.

20. Based on Mu et al., on Glass et al., and on my experience in molecular biology, IL-1 delta nucleic acids, such as SEQ ID NO:3 (or fragments thereof), can be used to detect cytogenetic rearrangements of the region of chromosome 2 to which IL-1 delta maps, which rearrangements are associated with physical abnormalities in Mu et al. and Glass et al. Such uses to detect rearrangements of the region of chromosome 2 to which IL-1 delta maps in patients provides a public benefit to those patients in currently available form.

21. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

By: _____
John E. Sims

Dated: 12/15/03

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